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Commentary

Braak Staging in Mouse Models of Alzheimer's Disease

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From the Department of Molecular Animal Physiology, Donders Center for Neuroscience and the Nijmegen Center for Molecular Life Sciences (NCMLS), Radboud University, Nijmegen; and the Departments of Molecular Neurobiology,[†] and Biological Psychiatry,[‡] University of Groningen, Haren, The Netherlands*

Alzheimer's disease (AD) is a heterogeneous multifactorial disease and is the most common progressive and aging-related neurodegenerative disorder. The major neuropathological features of AD are extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs), consisting of, respectively, aggregated amyloid- β peptide (A β) and hyperphosphorylated microtubule-associated protein Tau (MAPT). These histopathological lesions are mainly present in the hippocampus and the cerebral cortex, two large forebrain domains that are crucial for acquisition and storage of memory and other higher cognitive functions. The characteristic pathology eventually leads to the typical clinical symptoms associated with AD, such as general cognitive decline, dramatic memory loss, and severe personality changes. The most important risk factor for developing AD is advanced age. After the age of 65, the prevalence of AD in Western societies is forecast to double every five years (<http://www.alz.org>, last accessed August 15, 2010). By the age of 80, the number of patients suffering from AD is calculated to increase up to 40%.

An article in this issue of the *American Journal of Pathology* by David E. Hurtado and colleagues¹ reports on a new mouse model of AD, possessing A β and MAPT pathologies, which was created by the crossing of PS19 and PDAPP transgenic mice. These mice were characterized and staged for the occurrence of the NFT pathology in a spatiotemporal staging paradigm that is comparable to the Braak pathological stages of NFT in the human AD brain. Here, we provide a short survey of the mouse models that led to the article by Hurtado et al. Furthermore, we tried to highlight the importance and necessity of critical and systematic analyses, such as Braak-like staging in AD mouse models.

Even a century after the first description of the disease by Alois Alzheimer in 1907, the etiology of the disease is still poorly understood. However, several lines of evidence point to A β as the major factor in the pathogenesis of AD. The amyloid cascade hypothesis proposes that the A β peptides form toxic assemblies that initiate several processes, leading to neuronal dysfunction and eventually large-scale cell death.² The only definitive diagnosis of AD is made postmortem, the pathological hallmarks being extracellular amyloid plaques comprising A β , which is a cleavage product of the amyloid precursor protein (APP), and intracellular NFTs comprising hyperphosphorylated MAPT. This pathology shows a distinct spatiotemporal pattern, initially affecting areas of the temporal cortex, in particular the *trans*-entorhinal region, before extending to the hippocampus and certain other cortical zones. During the later disease stages, a more widespread pathology can be observed in frontal and temporal cortical areas and limbic regions.³ By processes that are not fully understood, the accumulation of A β and NFTs leads to injury of synaptic functioning between nerve cells and eventually produces massive local neurodegeneration, which ultimately accounts for the clinical signs of this disease.

The identification of genetic factors contributing to this disease has accelerated research on the biology of APP and MAPT, which has led to the generation of several transgenic mouse models that display some characteristic neuropathological features of AD, such as an age-dependent formation of amyloid plaques consisting of A β peptides.^{4,5} These models have been very important for our understanding of the complex pathogenic mechanism underlying AD.

Current transgenic models of AD rely almost exclusively on information gathered from inherited forms of the

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disease, which are far less common than sporadic forms, but are indistinguishable from a clinical and histopathological point of view. Despite the large quantity of transgenic AD mouse models in general, there is no ideal "complete" mouse model that incorporates all aspects of AD.

In the early 1990s, the first transgenic mice were generated by inserting the entire human APP gene into the mouse brain.^{6–9} Despite the successful expression of the APP gene product in the brain, these mice showed only very mild neuropathological changes, with only a few or no A β deposits. The lack of plaques in these transgenic mice was generally attributed to the insufficient expression of the transgene, the absence of mutations in the transgene, the genetic background of the mice, or to other unknown factors inherited by the mouse brain compared to the human.

The first mutant APP mouse model with robust plaque pathology was the PDAPP transgenic mouse. These mice express a human APP cDNA with the Indiana mutation V717F. Hemizygous mice begin to develop plaque pathology at the age of 6–9 months. These mice do not show NFT pathology and no neuronal loss but do show loss of synapses.¹⁰ Another mouse line with plaque pathology is the Tg2576 line, which expresses the mutant APP, which bears the Swedish mutation under the control of the hamster prion promoter. These mice develop plaque pathology from the age of 9 months on with cognitive deficits but without neuronal loss or NFT pathology.¹¹ Like the Tg2576 mice, the APP23 mice also express mutant APP containing the Swedish mutation, but under the control of the Thy-1 promoter.¹² This genetically manipulated mouse line shows prominent cerebrovascular amyloid pathology, amyloid plaques from the age of six months on, and some neuronal loss in the hippocampus. However, also in this transgenic mouse line, no NFT pathology has been observed.

Mice expressing either the wild-type or mutated presenilin-1 gene fail to develop significant AD-like pathology despite having high levels of A β .^{13–15} However, when mutant presenilin-1 mice are crossed with Tg2576 mice, A β aggregation into plaques is greatly accelerated.¹⁶ The absence of neuronal loss in most APP models suggests that physiological A β accumulation and subsequent plaque formation are not sufficient to cause rapid neuronal cell death *in vivo*. This in turn suggests that A β species alone are unlikely to cause widespread neuronal loss in the absence of major secondary pathogenic factors in human patients and is consistent with human neuropathological studies that show no correlation between overall levels of amyloid deposition and clinical progression of AD. One possible explanation may be the absence of NFT formation in the APP models and, hence, the missing link to massive neuronal cell loss in AD.

This view led to the development of several mutant mouse models with the characteristic Tau pathology to examine the particular role of MAPT in AD.

The first transgenic animal with marked tangle pathology and cell loss was the JNPL3 mouse, which expresses MAPT with the P301L mutation.¹⁷ This model could clearly demonstrate that MAPT alone can cause cellular damage and neuronal loss.

Htau transgenic mice express only human MAPT, because mouse MAPT was knocked out in this model.¹⁸ These mice accumulate hyperphosphorylated Tau at the age of six months and develop NFT pathology within 15 months of age.

Another mouse model with progressive NFT pathology and severe neuronal loss is the inducible MAPT transgenic line rTg4510.^{19,20} Abnormal MAPT pathology in these animals can already be observed at one month of age. Furthermore, these mice show cognitive deficits from 2.5 months forward. Cognitive performance improves if the transgene is turned off despite worsening NFT pathology.

Because most of these mentioned models show only one of the characteristic pathological features of AD, either A β or MAPT pathology, investigators began to cross mutant APP and MAPT transgenic mouse lines to obtain a mouse line with both pathological hallmarks of AD.

Such mice have significantly expanded our understanding of A β and MAPT pathologies. For instance, crossing the Tg2576 and the JNPL3 lines resulted in mice (TAPP) with increased MAPT forebrain pathology compared with JNPL3 mice, suggesting that either APP or A β can influence downstream MAPT pathology.²¹

Another prominent transgenic mouse line that accumulates both intraneuronal A β , extracellular amyloid plaques, and NFT lesions in an age-dependent fashion is the triple transgenic mouse model (3xTg-AD),²² which harbors preseniline-1 (M146V), APPswe, and MAPT (P301L) transgenes. These mice develop age-dependent synaptic dysfunction, including deficits of long-term potentiation, and memory deficits that correlate with an accumulation of intraneuronal A β .^{23,24} Probably the main observation obtained from this mouse model is that an excess of A β can elicit cognitive impairment even in the absence of NFT or neuronal loss.

Because of variations in neuropathologies and behaviors between transgenic mouse models and human disease, as well as among different transgenic lines, it is imperative to be cautious with comparing and interpreting results. Therefore, a standardized and critical analysis of information provided by genetic mouse models is needed to warrant quality and valuable preclinical research on AD neuropathology.

In the article by David E. Hurtado¹ and co-workers in this issue of the *American Journal of Pathology*, the authors developed a new mouse model for AD, which possesses A β and MAPT pathologies, by crossing PS19 and PDAPP Tg mice. These mice were characterized and staged for the occurrence of NFT pathology in a spatiotemporal staging paradigm comparable to the Braak pathological stages of NFT in AD human brains. This approach of MAPT pathology staging may help to explain the stereotypical manner in which the MAPT and A β pathologies appear, evolve, and spread over time with disease progression. Interestingly, their murine model of A β and MAPT pathologies shows a very similar sequence of pathological progression of AD MAPT pathology as observed in human AD patients. Furthermore, Hurtado and colleagues demonstrate that the presence of A β accelerates NFT formation and enhances MAPT pathology.

They also show that MAPT pathology does not have the same accelerating effect on A β pathology.

Their findings substantiate the amyloid cascade hypothesis of AD. According to this hypothesis, an accumulation of A β is the primary factor of AD pathogenesis. The Tau-related pathology of the disease process, including formation of NFTs, is proposed to result from an imbalance of A β production and A β clearance. The data presented in the study by Hurtado et al is in line with data from studies of 3xTg mice, which support the idea that MAPT pathology is a downstream event of A β accumulation. A recent study by Tomiyama et al demonstrated that A β oligomers are sufficient to cause synaptic alteration in addition to abnormal MAPT phosphorylation, glial activation, and neuronal loss *in vivo*.²⁵ Taken together, these findings reported here are important for our further understanding of the mechanisms underlying the onset as well as the progression of AD. However, to date, no transgenic mouse line has been able to represent all aspects of human AD pathology. This might be due to the limitations of rodent systems to reproduce a complex human disorder, such as AD, in which the pathogenesis usually takes several decades to manifest and primarily involves higher cognitive functions. Additional spatiotemporal staging of other histopathological features of AD, for example glial activation, cytokine release, or vascular changes such as reduction of cerebral blood flow, would provide additional valuable insights into the mechanisms of AD pathology for both basic and translational research.

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